REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-20 have been canceled. Claim 1 has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Restriction/Election

The Restriction Requirement requiring restriction to one sequence has been deemed proper and made Final. Applicants acknowledge the Examiner's action regarding the pending application and the claims.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 16-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is

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enabling for compounds 8 to 50 nucleobases in length that target and inhibit expression of fibroblast growth factor receptor 2 *in vitro* but suggests that the specification as filed is not enabling for *in vivo* uses of the claimed antisense compounds. The Examiner cites several articles on the technology of antisense to support the position regarding extrapolation to *in vivo* and pharmaceutical uses. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* as a pharmaceutical is unpredictable.

The Examiner has pointed to two articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

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The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The Examiner has also pointed to an article that discusses the role of fibroblast growth factors and their receptors in signaling. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects for these molecules is unpredictable.

However, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 16-20, with Applicants reserving the right to file a continuing application directed to this subject matter. Therefore, withdrawal of the rejection is requested.

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III. Rejection of Claims Under 35 U.S.C. 102

Claims 1 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Wilson et al. (GenEMBL Accession No. 132954). The Examiner suggests that this citation discloses a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to SEQ ID NO: 3 and since this primer contains all of the structural limitations of the claims is assumed to inherently possess antisense activity. Applicants respectfully traverse this rejection.

At the outset, Applicants have canceled claim 11 and amended claim 1, and by dependency claims 2 and 4-15, to recite that the compounds of the instant invention are targeted to specific regions of the human fibroblast growth factor receptor 2 nucleic acid molecule of SEQ ID NO: 3. Support for this amendment can be found throughout the specification as filed but in particular at pages 85-88 and Table 1.

Wilson et al. (GenEMBL 132954) disclose a 30 mer primer compound that is 100% complementary to nucleobases 1242 through 1271 of SEQ ID NO: 3 of the instant invention. Nowhere does this reference teach or suggest any antisense sequences as now claimed which are targeted to specific regions of fibroblast growth factor

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receptor 2. In order to anticipate an invention the paper cited must teach each and every limitation of the claims (MPEP 2131). Clearly, the cited reference cannot anticipate the invention of the amended claims and withdrawal of this rejection is respectfully requested.

Claims 1 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Wilson et al. (GenEMBL Accession No. 187104). The Examiner suggests that this citation discloses a 30 base pair fibroblast growth factor receptor 2 downstream primer and probe which is 100% complementary to SEQ ID NO: 3 and since this primer contains all of the structural limitations of the claims is assumed to inherently possess antisense activity. Applicants respectfully traverse this rejection.

Wilson et al. (GenEMBL 187104) disclose a 30 mer primer compound that is 100% complementary to nucleobases 1242 through 1271 of SEQ ID NO: 3 of the instant invention. Nowhere does this reference teach or suggest any antisense sequences as now claimed which are targeted to specific regions of fibroblast growth factor receptor 2. In order to anticipate an invention the paper cited must teach each and every limitation of the claims (MPEP 2131). Clearly, the cited reference cannot anticipate the invention of the

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amended claims and withdrawal of this rejection is respectfully requested.

Claims 1 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Chenchik et al. (GenEMBL Accession No. AR090312). The Examiner suggests that this citation discloses a 25 base pair keratinocyte growth factor receptor downstream primer and probe which is 100% complementary to SEQ ID NO: 3 and since this primer contains all of the structural limitations of the claims is assumed to inherently possess antisense activity. Applicants respectfully traverse this rejection.

Chenchik et al. (GenEMBL AR090312) disclose a 30 mer primer compound that is 100% complementary to nucleobases 1179 through 1203 of SEQ ID NO: 3 of the instant invention. Nowhere does this reference teach or suggest any antisense sequences as now claimed which are targeted to specific regions of fibroblast growth factor receptor 2. In order to anticipate an invention the paper cited must teach each and every limitation of the claims (MPEP 2131). Clearly, the cited reference cannot anticipate the invention of the amended claims and withdrawal of this rejection is respectfully requested.

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Claims 1, 2, 4, 5, 11 and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Yamada et al. (1999). The Examiner suggests that this reference discloses suppression of glioblastoma cell growth following antisense mediated inhibition of fibroblast growth factor receptor expression, as well as phosphorothioate antisense compounds complementary to the translation start site of fibroblast growth factor receptor 2 and their use in cells to reduce cell growth. Applicants respectfully traverse this rejection.

Yamada et al. (1999) disclose use of a phosphorothioate antisense oligonucleotide of unspecified length that was complementary to the translation start site of fibroblast growth factor receptor 2 and its use in cells to investigate the role of this molecule in signaling in human glioblastoma cells. Nowhere does this reference teach or suggest any antisense sequences as now claimed which are targeted to specific regions of fibroblast growth factor receptor 2, regions that do not include the translation start site. In order to anticipate an invention the paper cited must teach each and every limitation of the claims (MPEP 2131). Clearly, the cited reference cannot anticipate the invention of the

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amended claims and withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (1999), and further in view of Baracchini et al. (US Patent 5,801,154) and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to make antisense oligonucleotides as claimed because the art teaches the role of this molecule in cell growth regulation (Yamada et al.). The Examiner suggests that one of skill would have had a reasonable expectation of success based on the teachings of Yamada et al., while motivation to modify antisense is provided by the teachings of Fritz et al. and Baracchini et al. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims, as discussed *supra*, to list specific regions within the sequence of human fibroblast growth factor receptor 2 of SEQ ID NO: 3 that are to be targeted by antisense compounds, regions that do not include

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the translation start site. These regions are taught in the specification as filed at pages 85-88. As discussed in detail *supra*, the primary reference cited fails to teach or suggest use of antisense compounds targeted to the regions as now claimed.

The secondary references cited fail to overcome the deficiencies in teaching of the primary reference.

The '154 patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target specific regions of the human fibroblast growth factor receptor 2 (SEQ ID NO: 3) and the successful inhibition of expression using antisense.

Fritz et al. (1997) discloses cationic polystyrene nanoparticles as carrier systems for antisense compounds in general. This paper, however, does not teach or suggest use of antisense compounds of any type to target the human fibroblast growth factor receptor 2 (SEQ ID NO: 3), or any region within the sequence of this nucleic acid molecule, and the successful inhibition of expression using antisense.

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To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims as now amended, which specify specific regions within the sequence of fibroblast growth factor receptor 2 (SEQ ID NO: 3), are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art. It is only with the specification in hand that one of skill would understand that specific regions of fibroblast growth factor receptor 2 as claimed could be targeted successfully with antisense compounds. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

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V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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